UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/192,102	02/04/94	LE J	NYU93-01M

18M2/1220

DAVID E. BROOK
HAMILTON, BROOK, SMITH AND REYNOLDS
2 MILITIA DRIVE
LEXINGTON, MA 02173

EXAMINER	
NISBET	
ART UNIT	PAPER NUMBER
1806	18

DATE MAILED: 12/20/95

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary

Application No.	Applicant(s)
08/192,102	Le et al.
Examiner	**Group Art Unit**
T Michael Nisbet	1806

☒ Responsive to communication(s) filed on *11/21/94, 12/29/94, 1/30/95, 8/7/95, 12/6/95*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *91-97* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *91-97* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *14 &16*

☒ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☒ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

III. DETAILED ACTION

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The invention under examination is directed to a method of treating Crohn's disease in humans.

2. Applicant's attention is directed to the preliminary amendment filed 4/14/94 which amends the page numbering of the specification to coincide with that of the new sequence listing which was allegedly submitted with the 4/14/94 amendment. However, no sequence listing which corresponds in pages with the 4/14/94 amendment to the specification is currently in the file. In fact, the computer print out dated 4/21/95, which appears to correspond to the sequence listing cited in the 4/14/94 preliminary amendment, does not have 6 pages. However, the amendment to the specification requires that pages 150-157 be renumbered 150-156. Therefore, the sequence listing does not appear to correspond with amendment. Accordingly, clarification is requested and/or submission of a copy of the amendment in the original form.

3. Acknowledgement is made of the IDS filed 8/4/95 and 1/30/95. However, applicant's attention is directed to the fact that several references have been listed on the PTOL 892, but have not actually been provided. These citations have been crossed out on applicant's copy of the initialed 1449.

Double Patenting

4. Claims 91-97 are provisionally rejected under 35 U.S.C. 101, as claiming the same invention as that of claims 106-112 of copending application Serial No. 07/192,861. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The claims in each application are identical to one another. Therefore, one of ordinary skill in the art would not be able to practice the claims in one application without infringing the claims in the other application.

Priority

5. Applicant's specification makes reference to the priority application 07/670,827, 07/853,606, 08/013,413, and 08/010,406. However, the earliest applications fail to disclose the invention as presently claimed. Both the '827 and '606 cases failed to provide a disclosure of the claimed antibody in Crohn's disease. In fact, neither application even discloses Crohn's disease as a preferred embodiment. Consequently, the priority of the instant claims which refer to Crohn's disease only enjoy the benefit of parent application 08/013,413 which was filed 2/2/93.

Specification

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph as failing to teach how to make and/or use the invention, ie. failing to provide an enabling disclosure.

Given the precise nature of the antibody needed, deposit of cA2 pursuant to 37 C.F.R. 1.801-1.809 is required. It is noted that the Rademacher reference teaches that the specific glycosylation of the antibody is important in the instant case. It is noted that therefore, the exact antibody, cA2 is necessary to practice the invention in the instant case. Antibodies produced recombinantly will often have aberrant glycosylation or no glycosylation depending on the host in which said antibody is produced. Note that *E Coli* does not glycosylate and yeast do not N-glycosylate. Yeast O-glycosylate. Therefore, deposit of the hybridoma producing the antibody is required.

7. Claims 91-92, 94 and 96 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

8. Claims 93, 95, and 97 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the treatment of Crohn's disease with the cA2 antibody.

Undue experimentation would be required to practice the invention as claimed due to the quantity of experimentation necessary, the limited amount of guidance, and limited number of working examples in the specification, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or

unpredictability of the art, and the breadth of the claims. Ex parte Foreman, 230 USPQ 546, 547 (Bd. Pat. Appls. and Interf. 1986).

In the instant case, the specification provides no guidance as to the design of anti-TNF peptides which are able to bind with high affinity to TNF at residues 87-108 or residues 59-80 and 87-108, which competitively inhibit binding of Mab A2, and which can neutralize biological activity of TNF α with an ID50 as specified in claims 49-51. The specification describes an analysis of the epitope binding specificity of exemplary monoclonal antibody A2. However, there is no description of the structural elements required of a peptide which have the above characteristics which would provide guidance to one of skill in the art in the production of immunoreceptor molecules as broadly defined by claim 35. The ability to produce the broadly claimed molecules would constitute a significant burden of experimentation for which the specification provides no conceptual support and no exemplification.

Murch teaches that TNF alpha is elevated only in individuals with large bowel Crohn's disease. See abstract, and pages 914, last paragraph, as well as 915, left col., second paragraph. Indeed, the reference teaches one skilled in the art that the concentration of TNF does not always correlate with the disease state. In fact, page 914, last paragraph states that "relapse of small bowel Crohn's disease alone, with no evidence of colonic involvement, was not associated with a significant rise in TNFα above control values...". Moreover, the reference states at page 915, rt. col., para. 4, that:

"Populations of histiocytes and macrophages with different morphology and biochemical activity have been found in the small bowel compared with the colon."

and at page 915, rt. col., third paragraph:

"Most TNF α is produced in activated macrophages and monocytes..."

Consequently, the state of the art at the time the application was filed shows that different populations of macrophages are responsible for producing the diseases in small and large bowel disease. It is noted that page 117, line 20 of the specification indicates that the ileum (small intestine) contained an "irregularity" prior to treatment with steroids. This led to a remission in the ileal "irregularity" because page 118, line 10 and following showed that the terminal ileum was "normal". Consequently, applicant's data seems to support what is shown by the state of the art as represented by Murch *et al.*. That is that the aetiologies of small and large bowel Crohn's are different with respect to serum TNF levels and treatments of one type of disease does not work for the other. Consequently, objective factual evidence exists to doubt the enablement of the invention with respect to small bowel Crohn's disease. Therefore, undue experimentation would have been required to practice the small bowel embodiment of Crohn's disease at the time the application was filed.

Further review of the art reveals that the ~~application~~ claims should be limited to the particular antibodies which have been demonstrated to effectively treat Crohn's, cA2. To begin with, the A2 antibody is a murine monoclonal antibody. The state of the art

at the time the invention was filed was rife with failed clinical trials using murine antibodies alone. It is well established that the human body will mount a strong HAMA response to murine antibodies which are administered *in vivo*. Furthermore, in the instant case, the nature of the invention is drawn to treatment of an autoimmune disorder in which the body's immune system is already hypersensitive. Consequently, any normal HAMA response would reasonably be expected to be more severe than normal. Furthermore, the repeated failure in the past at treating humans with foreign proteins renders the instant invention extremely unpredictable. Given the state of the art, the nature of the invention, and unpredictability of the disease, undue experimentation would be required to practice the instant invention with any other antibody other than cA2

Furthermore, applicant's attention is directed to the Rademacher reference which shows that the glycosylation of the antibody is extremely important in treating individuals with any allergic disorder, and Crohn's disease in particular. Specifically note the teachings of the reference at page 231 which states that "changes in oligosaccharides may in some cases,..contribute directly to disease pathogenesis". Furthermore, page 234 shows that Crohn's disease is specifically associated with the aberrantly deglycosylated G(O) type of antibody. See Figs 2 and 5b as well. Fig 5b specifically teaches one skilled in the art that the percentage of agalactosyl monosaccharide sequence in IgG relates directly with the onset of Crohn's disease. Finally, the reference teaches that the carbohydrate structure of the antibody can

effect different functions depending on the type of carbohydrate moiety. Applicant's specification is completely devoid of guidance with respect to the kinds of glycosylation one skilled in the art should consider in effectively treating Crohn's disease. Moreover, applicant's specification at page 11, line 32 teaches that the preferred cA2 antibody is indeed of the IgG_1 subclass. Consequently, the results of the Rademacher reference apply directly to the instant application. In conclusion, applicant's specification fails to provide one skilled in the art with the requisite road map to guide the routineer to make and/or use antibody subtypes with the proper glycosylation. Consequently, absent such guidance, Rademacher provides objective factual data to believe that such guidance is either unnecessary or within ordinary skill in the art. The examiner has set forth "sound scientific reasoning" regarding the basis of the rejection under 35 U.S.C. § 112, first paragraph. Ex parte Hitzemann, 9 USPQ 2nd, 1821, 1822 (Bd. Pat. Appls. and Interf. 1988). In Hitzemann, the Board stated:

> "with respect to the prima facie case of non-enablement, we note that a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more is required. Id. at 1823.

Therefore, based on the state of the art as set forth in Rademacher, the unpredictability of treating physiological reactions set forth by *Hitzemann*, cit. omitted,

and the lack of guidance in applicant's specification, undue experimentation would be required to practice the invention with other antibodies besides cA2.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10. Claims 91-97 are rejected under 35 U.S.C. § 103 as being unpatentable over Lichtenstein in view of Sun in further view of Le, WO9102078, or Moller.

The claims are drawn to a method of treating Crohn's disease through the administration of a therapeutically effective amount of an anti-TNF antibody. The

dependent claims recite the use of the specific epitopes corresponding to the antibodies and to specific antibodies themselves, eg A2 and cA2.

The Lichtenstein reference teaches the involvement of TNF alpha in etiology of Crohn's disease (see abstract). The reference teaches one of ordinary skill in the art that Crohn's disease is associated with elevated levels of TNF alpha and indicates that TNF alpha is present in highest concentrations at the site of necrosis.

The Sun reference teaches that TNF alpha is specifically involved at the cellular level in bowel necrosis (see title for example). Moreover, the Sun reference teaches at the cellular level, that TNF alpha can play a causative role in bowel necrosis. See page 1330, last paragraph, right col.. Moreover, TNF is taught to be "a major cytokine that may initiate a cascade of inflammatory and coagulative events in...tissue injury.....and...may play an important role in the development of irreversible shock and bowel necrosis". (c.f. page 1330, last paragraph). Moreover, the paragraph bridging pages 1329 and 1330 teaches one of ordinary skill in the art that TNF mediates PAF release. Therefore, the Sun reference would have taught one of ordinary skill in the art that anything that inhibits TNF would also inhibit PAF, because PAF is released by serum TNF. Moreover, the reference teaches at the last sentence of the abstract that "TNF-induced bowel necrosis is due to PAF release and can be prevented by pretreatment with PAF antagonists". See also the last paragraph of page 1329. Therefore, the reference clearly suggests to one of ordinary skill in the art that inhibition of TNF inhibits bowel necrosis. Accordingly, the reference provides a

reasonable expectation that molecules which inhibit TNF action *in vivo*, would also inhibit diseases associated with bowel necrosis. Crohn's disease is just such a disease.

The Le reference teaches the preferred antibodies of the invention as claimed. Specifically, the A2 and cA2 antibodies are taught by the abstract. In addition, the antibodies are taught to be useful in pathological conditions associated with TNF alpha and "for removing TNF alpha from body fluids". The Le reference does not contain any teachings concerning it's use for inflammatory bowel diseases such as Crohn's disease.

The Moller references teach monoclonal antibody M195 which appears to be the same as the antibody of the present invention. M195 is functionally similar to the A2 antibody as characterized in the specification, in exhibiting high affinity binding to TNF-alpha, neutralizing TNF-alpha but not TNF beta (see p. 164, Table 2) binding to human and chimpanzee TNF but not TNF from baboon, rhesus monkey or cynomolgus monkey (eg. Cytokine, p. 164,. col.1)In view of those similarities, the A2 and M195 antibodies appear to have the same or similar epitope binding specificities and M195 antibodies appear to have the same or similar epitope binding specificities and M195 is expected to have the properties recited in the instant claims.

WO9102078 teaches high affinity TNF-specific monoclonal antibodies which bind to neutralizing epitopes. Certain of these antibodies bind to epitopes located within synthetic peptides corresponding to TNF-alpha, which contain an epitope

recognized by the A2 antibody. According to the teaching of the specification the A2 antibody binds to synthetic residues comprising residues 87-108 and 59-80. According to the teaching on page 33 of the reference, Mab1 binds to a peptide consisting of residues 58-65, Mab11 binds to a peptide consisting of residues 49-96, Mab54 binds to a peptide consisting of residues 49-56-79, etc. Results of competitive binding assays using the referenced antibodies are shown in Fig 9. The antibodies are shown to inhibit biological activities of TNF alpha according to the teachings in Table 2, page 22. At least some of the referenced antibodies would be expected to competitively inhibit binding of Mab A2 of the instant claims to TNF alpha and to have ID50 values recited in the claims.

The antibody references of Le, Moller, and WO91/02078 do not teach the use of anti-TNF antibodies for treating Crohn's disease.

However, the prior art of Le teaches the preferred antibody, cA2, and that said cA2 is useful in removing TNF alpha from body fluids. Both the Moller references teach M195 which is the parent monoclonal antibody from which cA2 was produced. The prior art Sun and Lichtenstein and also teach that TNF alpha is associated with Crohn's disease at both the systemic (Lichtenstein) and cellular (Sun) levels. Moreover, Sun establishes a causal link between the level of *in vivo* TNF concentration and the degree of bowel disease and that any inhibitor of TNF would also inhibit bowel disease. Consequently, knowing that cA2 or A2 can remove TNF from body fluids and knowing that removing TNF from serum would inhibit the *in vivo*

effects of TNF because there would be a lower concentration of TNF in solution, one of ordinary skill in the art would be motivated to use cA2 or A2 to treat Crohn's disease with a reasonable expectation of success. As a result, the invention as claimed would have been clearly *prima facie* obvious to one of ordinary skill in the art at the time that application was filed absent unexpected results.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Nisbet whose telephone number is (703) 308-4204 from 9:00 am to 5:00 pm weekdays with the exception of alternating Mondays. If the examiner cannot be reached, the supervisor, Marion Knode, may be contacted at phone number (703)308-4311.

The number for facsimile submission of papers has changed. The new fax number for Art Unit 1806 is (703) 305-7401. Please provide the serial number, application title, examiner's name, and art unit on the fax cover sheet to expedite clerical processing. In addition, all cover sheets should be marked **DRAFT** or **OFFICIAL** as appropriate.

Any informal communications of a **nonconfidential** nature can be communicated to Examiner Nisbet electronically at the following address, tnisbet@uspto.gov.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

LILA FEISEE
PRIMARY EXAMINER
GROUP 1800

08/192,861

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO./TITLE

DATE MAILED:

NOTICE OF INFORMAL APPLICATION

(Attachment to Office Action)

This application does not conform with the rules governing applications for the reason(s) checked below. The period within which to correct these requirements and avoid abandonment is set in the accompanying Office action.

A. A new oath or declaration, identifying this application by the application number and filing date is required. The oath or declaration does not comply with 37 CFR 1.63 in that it:

1. ☐ does not identify the city and state or foreign country of residence of each inventor.
2. ☐ does not identify the citizenship of each inventor.
3. ☐ does not state whether the inventor is a sole or joint inventor.
4. ☐ does not state that the person making the oath or declaration:
   a. ☐ has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.
   b. ☐ believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought.
   c. ☐ acknowledges the duty to disclose information which is material to the examination of the application in accordance with 37 CFR 1.56(a).
5. ☐ does not identify the foreign application for patent or inventor's certificate on which priority is claimed pursuant to 37 CFR 1.55, and any foreign application having a filing date before that of the application on which priority is claimed, by specifying the application serial number, country, day, month, and year of its filing.
6. ☒ does not state that the person making the oath or declaration acknowledges the duty to disclose material information as defined in 37 CFR 1.56(a) which occurred between the filing date of the prior application and filing date of the continuation-in-part application which discloses and claims subject matter in addition to that disclosed in the prior application (37 CFR 1.63(d)). → 08/010,406 filed 01/29/93
7. ☐ does not include the date of execution.
8. ☐ does not use permanent ink, or its equivalent in quality, as required under 37 CFR 1.52(a).
9. ☐ contains non-initialed alterations (See 37 CFR 1.52(c)).
10. ☒ Other: Priority as continuation-in-part of 08/010,406, filed 01/29/93 is not claimed in declaration.

B. Applicant is required to provide:

1. ☐ A statement signed by applicant giving his or her complete name. A full name must include at least one given name without abbreviation as required by 37 CFR 1.41(a).
2. ☐ Proof of authority of the legal representative under 37 CFR 1.44.
3. ☐ An abstract in compliance with 37 CFR 1.72(b).